REMARKS

I. Preliminary Remarks

Amended claim 84 is directed to methods for assaying for modulators of β-secretase activity, comprising contacting a polypeptide with β-secretase APP processing activity with a substrate, wherein said substrate comprises an APP molecule having a modified β–secretase processing site defined by the formula P_2P_1-$P_1'P_2'$. Methods utilizing an APP molecule with a modified APP processing site are supported in the specification at page 8, lines 4-8 and Example 5 (pages 86-87). The additional claim amendments put the dependent claims in conformity with amended claim 84 or improve dependencies. These claim amendments do not add new matter to the application.

II. Rejection Under 35 U.S.C. § 112, First Paragraph Should be Withdrawn

Claims 84-107 were rejected under 35 U.S.C. § 112, first paragraph for lack of adequate written description. In particular, the Examiner stated that the state of the art and the description in the specification suggests that Applicants were not in possession of the claimed invention at the time of filing. Applicants traverse this rejection.

According to the United States Patent and Trademark Office Revised Interim Written Description Guidelines, a specification provides an adequate written description of a genus if a representative number of species are implicitly or explicitly disclosed. What constitutes a "representative number of species" is determined by what one of skill in the art would recognize as possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed or claimed (see page 9 of Written Description Guidelines, 66 Fed. Reg. 1099, 2001).

A. Analysis of the Claimed Subject Matter and Descriptive Support in the Application

At the outset, it is important to fairly characterize the scope of the genus that is at issue in the application, focusing on the necessary common attributes. The claims recite a substrate that is an APP molecule that has a modified β-secretase processing site. The modified β-secretase processing site is defined by the formula of P_2P_1-$P_1'P_2'$. The amino acid sequence of APP molecules are well known in the art and the specification teaches that at least 3 APP isotypes (wild-type, 695 amino acids and 770 amino acid) exist. See page 2

lines 6-11. Example 5 (pages 86-87) is a working example in which the β-secretase processing site of the 695 amino acid APP isotype (amino acids 594-597) has been modified from KM-DA to SY-EV or SY-EA. As shown in Figure 3, human Asp2 proficiently cleaved APP at each of the modified processing sites. Therefore, the specification teaches how to modify APP at the β-secretase processing site and demonstrates that modifications within the processing site retain function. Furthermore, post-filing publications teach that modifications in APP at the β-secretase processing site are functional. (See attached PCT Publication Nos. WO 2004/099376 and WO 2004/111189).

The genus of modifications of the processing site of APP is a defined genus in which 4-8 residues defining the β-secretase cleavage site are varied. The number of variations are well defined and predictable because the possible substitutions are defined in the claim. However, the genus of modifications within the known APP sequence is orders of magnitude narrower than the genus of any possible modifications within the full length amino acid sequence of APP.

While the genus may seem large in some contexts, it is a pittance in the fields of chemistry and molecular biology, where automated synthesis techniques, recombinant techniques, and high throughput screening techniques (to name just a few) abound, making manipulation and testing of large numbers of molecules a common occurrence. In view of the guidance in the specification and the known properties of conservative amino acid substitutions, the total number of possible species is less than what the Patent and Trademark Office routinely issues in connection with an allowance of a typical genus claim in a specification directed to traditional organic chemical pharmaceuticals. The written description training materials approve of this practice, *e.g.*, by approving of claims to a genus of biomolecules by "percent identity" to a reference sequence, together with a limitation of function.

The present application also teaches activity assays that can be used to select from the genus of peptides satisfying the structural limitations of the claims only those peptides which also satisfy the functional limitations of the claims, namely, that the peptide is cleaved by an enzyme of interest (β-secretase). Through the combination of structural and functional limitations, the claims read only on "active" (cleavable) substrates. Through the

teachings of assays, the application permits identification of the cleavable substrates through nothing more than routine screening.

In addition, the specification exemplifies 48 species that are encompassed by the claimed genus (see page 20, lines 5-14, page 21, lines 12-22, page 24, lines 3-10, page 25, lines 1-14, page 26, lines 3-25). The specification provides data to demonstrate that 26 of the disclosed species are cleaved between the P_1 and $P_{1'}$ residues by a human aspartyl protease. Further, the specification provides a number of exemplary species based on the teachings in Table 6 (page 303, lines 5-15). The specification also teaches one of skill in the art how to test any possible species for cleavage by a human aspartyl protease. (*See, e.g.*, page 79, lines 30 through page 81, line 14). The disclosed species, the disclosed formula to generate species that possess the structural requirements of the genus and the teaching of screening assays to measure aspartyl protease cleavage of any substrate demonstrate that the Applicants were in possession of the claimed genus at the time of filing. Post-filing publications also demonstrate that species encompassed by the claimed genus are functional, *e.g.* see U.S. attached Patent No. 7,132,401 (Table 3), attached PCT Publication No. WO 02/094985 (page 41, lines 19-25) and PCT Publication No. WO 2004/099376 (page 7, lines 21-24).

B. Claims are Limited to Functional Peptide

In addition to the structural requirements recited in the amended claims, the claim are limited by functional language so as only to encompass working embodiments. Even if the claims did read on inoperative embodiments, the law says that there is no requirement that every possible substrate amino acid sequence encompassed by the claimed genus be operable. It is not the function of the claims to specifically exclude possible inoperative substrates, and undue experimentation depends on whether the number of inoperative substrates becomes significant. *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co. and Alamo Explosives Co. Inc.* 750 F.2d 1569, 1576 (Federal Circuit 1984).

The Examiner cites references (Gruninger-Leitch *et al. J. Biol. Chem.* 277: 4687-4693, 2002, Suader *et al. J. Mol. Biol.* 300: 241-248 and Vassar *et al., Science* 286: 735-741, 1999) to illustrate that a single point mutation within a substrate can dramatically reduce protease cleavage of that substrate. As the claims are only directed to substrates that are cleaved by a human aspartyl protease encoded by the nucleic acid sequence of SEQ ID

NO: 1 or SEQ ID NO: 3, teachings regarding substrates that are not cleaved (and not claimed) are not relevant to a written description analysis of what is claimed. As stated above, the specification teaches activity assays that can be used to determine whether a substratethat satisfies the structural limitations of the claims is cleaved by a human aspartyl protease sequence and these methods of screening are well known in the art.

C. Response to Specific Points Raised by the Examiner

In the Office Action, the Examiner cited teachings in the art to support his statement that one of skill in the art would doubt that Applicants had adequately described the invention as broadly claimed. Quite to the contrary as explained below, these documents, which were published after the filing date of the present application, illustrate that one of skill in the art would agree that the present application adequately describes the necessary common attributes or features of the elements possessed by the members of the genus. For example, Gruninger-Leitch *et al.* (*J. Biol. Chem.* 277: 4687-4693, 2002) provides 7 modified or artificial APP β-secretase cleavage sites that were cleaved by a human aspartyl protease. In addition, Shi *et al.* (*J. Alzheimer's Disease* 7: 139-148, 2005) tested the activity of 24 mutate APP substrates and all but one were cleaved by β-secretase. These examples demonstrate that those of skill in the art routinely use methods similar to those described in the specification to identify functional substrates for human aspartyl proteases. Therefore, there is a reasonable expectation that carrying out the methods described in the specification will be successful in identifying substrates that are cleaved by a human aspartyl protease. The identification of additional functional substrates in post-filing references, such as Gruninger-Leitch *et al.* and Shi *et al.*, promote a likelihood of success rather than reasons to doubt that carrying out the methods described as the invention are unpredictable.

The Examiner considers methods for designing substrates by focusing on the P_2P_1-$P_1'P_2'$ residues to be unpredictable. However, these methods are routine to those of skill in the art and have been used by regularly in the art to design substrates. (See Gruninger-Leitch *et al.*, Shi et al., Sauder et al., Tomasselli *et al.*, Turner *et a/ Biochemistry* 40: 10001-10006, 2001, US Patent No. 7,132,401 (attached) , PCT Publication NO. WO 02/094985 (attached)). The substrate design may be extended out to the P4, P3 , P3' or P4' residues but

a review of the art demonstrates that the skilled artisans do not concern themselves with the residues more distant from the cleavage site.

In particular, the Examiner stated that Gruninger –Leitch *et al.* teaches that the specificity and activity of a number of substrates cleavable by BACE are effected by the following factors: 1) the amino acids further from the scissile bond of the substrate, such as P_4, P_3, $P_{3'}$ and $P_{4'}$, 2) the length of the substrate required for cleavage by the substrate enzyme and 3) certain *in vitro* and *in vivo* differences in activity. The Examiner pointed to Table 1 of Gruninger-Leitch *et al.* to illustrate that a single change to the amino acid sequence of a substrate may result in a decrease in cleavage activity. However, all substrates set out in Table 1 of Gruninger-Leitch *et al.*, that were designed to be cleaved by the β-secretase enzyme, exhibited some activity. The inactive substrates were either designed to be cleaved by α-secretase or renin, and these substrates are not encompassed by the claimed genus of peptides.

The Examiner pointed to examples in Gruninger-Leitch *et al.* which demonstrate that a single point mutation at the $P_{1'}$ or P_4 of the Swedish mutant cleavage site results in a drop in the rate of cleavage. It is inappropriate to assert that substrates cleaved at a lower efficiency do not support the claimed genus when this measured efficiency was determined by a comparison of cleavage of the highly efficient "Swedish mutation" substrate. Even the wild-type substrate has only 9% cleavage compared to the Swedish mutation, yet it can be used in assays. Claim 84 only require that the substrates for use in methods of the invention be cleaved by a human aspartyl protease, and all of the substrates for use in the claimed methods are cleaved at a useful rate. Furthermore, claim 100 is limited to substrates that are cleaved at a rate greater than the rate of cleavage of the wild-type APP processing site (SEVKM-DAEFR), and claim 101 is limited to substrates that are cleaved at a rate greater than the rate of cleavage of the "Swedish mutation" (SEVNL-DAEFR). Thus, the Examiner's concerns regarding predictability do not apply to claims 100 and 101.

However, it is unfair to assert that substrates cleaved at a lower efficiency do not support the claimed genus when this measured efficiency was determined by a comparison of cleavage of the highly efficient "Swedish mutation" substrate. The authors of the Gruninger-Leitch *et al.* study does not subscribe to or agree with the Examiner's

interpretation of Gruninger-Leitch data because the author's reach conclusions such as, "[t]he data presented above also indicates that BACE can accept a wide variety of peptidic substrate." (Gruninger-Leitch *et al.* page 4692, bottom of right column.) and "[t]he results of the present investigation further indicate that BACE1 can accept a wide variety of amino acid residues at the β-scissile-bond of its substrate both *in vitro* and in cells." (Shi *et al.* page 146, left column). A reading of Gruninger-Leitch *et al.* and other references cited by the Examiner indicates that the state of the art recognizes that the art substantiates that functional substrates can be designed by focusing on the P_2P_1-$P_1'P_2'$ positions within the substrate. In addition, these references also illustrates that those of skill in the art agree that focusing on the core cleavage-site residues as the Applicants have done, rather than distant residues is a proper approach for substrate-discovery.

In addition, the Examiner stated that the approach for identifying substrate peptides taught in Gruninger-Leitch *et al.* demonstrates that the certain combinations of amino acids within the cleavage site seem to be interdependent and that *in vivo* and *in vitro* differences affect activities. These factors are not evidence that the claimed substrates are not functional nor do these factors demonstrate that the substrate identification methods taught in the specification would be unsuccessful. The majority of the substrates taught in Gruninger-Leitch *et al.* are cleaved by BACE as some rate, and 3 out of the 5 of the substrates with low cleavage rates (0 – 2% cleavage of best substrate) were controls that were not expected to be cleaved by BACE (See Table 1, page 4689). Further, the approach taught by Gruninger *et al.* did not identify the substrates resembling wild-type APP, from which it was concluded that wild-type APP is not a preferred substrate for BACE in their *in vitro* assay (Gruninger-Leitch *et al.* page 4690). This indicates that their screening procedure might be questionable as it did not identify any substrates based on the wild-type APP cleavage site.

The Examiner also cited Majer *et al.* (*Protein Science* 6: 1458-1466, 1997) as further support that additional important considerations besides the P_2P_1- $P_1'P_2'$amino acid residues exist and amino acid substitutions are not additive. However, Majer *et al.* describes the development of inhibitors of the aspartyl protease cathepsin D based on subsite specificity. Pepstatin A is a known inhibitor of cathepsin D activity and Majer *et al.* therefore used as the lead compound for development of novel inhibitors. The residues denoted as Pn (P_4, P_3, P_2, P_1, P_1', P_2', P_3', and P_4') in Majer *et al.* refer to amino acid side

chains that bind of the inhibitor that interact within the corresponding Sn subsites with the cathepsin D active site. (See Fig. 2 Baldwin *et al. Proc. Natl. Acad. Sci.* 90: 6793-6800, 1993).

These Pn designations in Majer *et al.* differ from the Pn designations in the specification and the pending claims. As stated at page 19, lines 1-7 of the specification, Pn refers to amino acid residues in the peptide substrate that undergo cleavage. The amino acid residues of the N-terminal side of the scissile bond are numbered P_3, P_2, P_1 and those residues of the C-terminal side are numbered $P_{1'}$, $P_{2'}$, $P_{3'}$ and the P_1 or $P_{1'}$ residues are those residues located near the scissile bond (the bond that is cleaved by the enzyme). See Schelcter and Berger, B*iochem. Biophys. Res. Commun.* 27: 157, 1967. In Majer *et al.*, the P_1 and $P_{1'}$ residues are those near the central statine residue of pepstatin which is not a cleavage site because pepstatin is not cleaved by cathepsin D. In addition, the enzymatic activity measured in Majer *et al.* is inhibitory potency rather than cleavage by the protease. Even though similar nomenclature is used in the specification and Majer *et al.*, the teachings in Majer *et al.* are not relevant to the present invention. Furthermore, Majer *et al.* is less relevant in view of the studies in Gruninger-Leitch *et al.*, which repeatedly state that BACE has a loose substrate activity and that the BACE protease accepts a wide variety of peptide substrates.

In view of the foregoing remarks, claims 84-93 and 96-107 are adequately described in the specification. Applicants request that the rejection under 35 U.S.C. § 112, first paragraph for lack of written description be withdrawn.

III. Double Patenting

Claims 84-107 were provisionally rejected under 35 U.S.C. § 101 as claiming the same subject matter of claims 84-107 of co-pending application nos. 10/801,487 and 10/801,509, claims 43, 49, 58-60, 64 and 66 of co-pending application no. 10/801,486 and claims 102-131 of co-pending application no. 09/908,943. As noted by the Examiner, the claims in the co-pending applications have not yet been allowed and these rejections are provisional. Upon notice of allowance of any one of the cited co-pending applications, Applicants will amend the claims as necessary to ensure that the same invention is not claimed in more than one patent.

CONCLUSION

In view of the foregoing amendment and remarks, Applicants believe claims 84-93 and 96-107 are in condition for allowance and early notice thereof is requested.

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